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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,550	CHENCHIK ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *17-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/03; 12/28*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

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DETAILED ACTION

1. This action is in response to the papers filed July 22, 2005. Currently, claims 1-25 are pending. Claims 17-25 have been withdrawn from consideration.

Election/Restrictions

2. Applicant's election of Group I, Claims 1-16 in the response filed July 22, 2005 with traverse is acknowledged. The response asserts that the search of the entire application may be made without serious burden. This argument has been reviewed, but not found persuasive because a search of the array and a search of the assay are patentably distinct and would require a separate search.

Priority

3. This application claims priority as a continuation of 09/750,452, filed December 27, 2000 and 09/298,361, filed April 23, 1999 as a continuation in part.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-16 are indefinite over the recitation "said control pool of target nucleic acids" in line three of Claim 1. "Said control pool of target nucleic acids" lacks proper antecedent basis. It is noted that the claim does refer to a "control set of target nucleic acids" but the claim does not discuss a "control pool". Therefore, it is unclear how a control set and a control pool differ. This rejection may be easily overcome by amending the claim such that the two phrases coincide.

B) Claims 1-16 are indefinite over the recitation "at least 20 distinct target nucleic acids" because it is unclear whether the claim is referring to the test set of target nucleic acids or the control set of target nucleic acids. Based upon the claim language and the reading the claim in light of the specification, it is most likely that the phrase is intended to recite "at least 20 distinct control set target nucleic acids". Therefore, the rejection may be easily overcome by amending the claim to modify target nucleic acids.

C) Claims 2-3, 7 are indefinite over the recitation "at least a subset of the probe nucleic acids present on said array" because "the probe nucleic acids", in Claim 2, lacks antecedent basis. There is no indication of "the probe nucleic acids".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-6, 8-10, 13-14, 16 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Brown et al. (US Pat. 5,807,522, September 15, 1998).

Brown et al. (herein referred to as Brown) teaches an array based hybridization assay which contacts an array with two sets/pools of target nucleic acids, a test sample and a control sample. The control sample of nucleic acids comprises at least 20 distinct nucleic acids such that each of these nucleic acids are of known sequence and known amount. The hybridization patters of the target nucleic acids are detected. Specifically, Brown teaches a method of detecting differential expression of each of a plurality of genes in a first cell type with respect to expression of the same genes in a second cell type (col 4, lines 52-55). Brown teaches that there is "first produced fluorescent-labeled cDNAs from mRNAs isolated from the two cells types, where the cDNAs from the first and second cell types are labeled with first and second different fluorescent reporters (col 4, lines 55-60)(limitations of Claim 5, 9, 10). Brown teaches simultaneously adding "a mixture of the labeled cDNAs from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array (col 4, lines 60-65)(limitations of Claim 14). The array is then analyzed for hybridization patterns by detection of fluorescence (col 4, lines 65-67). Brown teaches that the relative expression of known genes in the two cell types may be determined by the

observed fluorescence emission color of each spot (col 5, lines 4-8)(limitations of Claim 13). In a specific example provided by Brown, a 0.5 cm x 0.5 cm microarray of 24 cDNA clones, where the microarray was hybridized simultaneously with total cDNA from wild type Arabidopsis plant labeled with a green fluorophore and total cDNA from a transgenic Arabidopsis plant labeled with a red fluorophore (col 5, lines 46-55, Figure 8)(limitations of Claim 6). Two micrograms of the cDNA products from each type of plant were pooled together and hybridized to the cDNA clone array, known amount of the pool of control set of target nucleic acids (col 17, lines 65-68). As provided in Example 2, the genes "equally expressed in wild type and the transgenic Arabidopsis appeared yellow due to equal contributions of the green and red fluorescence to the final signal. The does are different intensities of yellow indicating various levels of gene expression, indicating in the control sample (wild type sample), 23 of the known cDNA clones were present to some extent (limitations of Claim 1, 2). A single cDNA clone representing the transcription factor HAT4, expressed in the transgenic line of Arabidopsis but not detectably expressing in wild type, appears as a red dot, indicating that the concentration of the test target nucleic acid, namely wild type, would be minimal (limitations of Claim 16). In the event that the transgenic plant sample was considered to be the control sample, all of the spots (probe nucleic acids present on the array) would have appeared in the control sample (limitations of Claim 3). With respect to Claim 4, in the event that "the same label" is deemed to encompass fluorescent labels, both pools of nucleic acids were labeled with the same label, a fluorescent label, as

opposed to a radioactive or calorimetric detection means. Brown teaches that the first two and the last four elements of each array are positive controls for the detection step.

6. Claims 1, 4-10, 13, 16, 26-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Bao et al. (US Pat. 6,251,601, filed February 2, 1999).

Bao et al. (herein referred to as Bao) teaches a method of simultaneous measurement of gene expression and genomic abnormalities using nucleic acid microarrays. Bao teaches a method comprising contacting an array with a plurality of probes with a test set and a control set of target nucleic acids. The control set comprises at least 20 distinct control target nucleic acids of known sequence and known amount and all of said probe nucleic aids are present on said array are present in the control set. Specifically, Bao teaches contacting at least three labeled probes nucleic acid populations with an array such that each of the populations are labeled in a fluorescent color (col. 6, lines 35-45)(limitations of Claim 4-5). All of the populations are labeled with a fluorescent label (limitations of Claim 4). Moreover, each of the populations is labeled with a different fluorescent color (limitations of Claim 5). Bao teaches that "measurement and comparison of hybridization of message, genomic and reference nucleic acids at the same target elements provides the simultaneous assessment of expression and genomic changes." This inherently implies that each reference nucleic acid is present on the array. As seen in Figure 2d-f, bar graphs of the ratios of cDNA and genomic to reference sequences for various genes is exemplified. Bao teaches that an array of 31 target elements is exemplary, but the number of target

elements and the complexity of the nucleic acids determines the density (cool. 8, lines 1-5). Bao teaches that the reference nucleic acids can be "spiked" to include a known amount of a particular genomic or cDNA sequence, i.e. known amount and known sequence for each of the controls. Bao teaches that the quantities of each labeled tissue nucleic acid and reference nucleic acid to be used are preferably in the range of about 100ng to about 1ug (col. 13, lines 25-31)(limitations of Claim 26). The tissue and reference nucleic acid populations are hybridized to the array under suitable hybridization conditions (col. 13, lines 32-35). Bao analyzes the microarray by determining the intensity of each of the target spots. Bao teaches that the value "D" is for the reference intensity (col. 17, lines 22-25). Bao provides numerous formulas for determining the normalized presence of the nucleic acids (col. 18). For the specific example provided by Bao, the fluorescence ration for the Colo 320 compared to the reference is depicted in Table 3. Table 3 illustrates that the fluorescence of each of the targets on the array were present in the control set since a ratio was determined (limitations of Claim 13, 16). Bao teaches that the gene amplification observed with three probes hybridized simultaneously to one chip was similar to that obtained by separate hybridizations of DNAs onto separate chips (col. 28, lines 25-28). Bao teaches that "with the use of total human genomic DNA as a reference for expression analysis in the methods of the invention, the expression profiles of different samples can be compared even if the assays are carried out separately and independently" (col. 34, lines 25-32)(limitations of Claim 6-8). Therefore, since the method of Bao is directed a reference set of nucleic acids (control) which are present in known amount and are of

known sequence and all of the probes present on the array are represented in the control set, as exemplified by the ratios determined, the instant claims are anticipated by the teachings of Bao.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 7, 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US Pat. 5,807,522, September 15, 1998).

Brown et al. (herein referred to as Brown) teaches an array based hybridization assay which contacts an array with two sets/pools of target nucleic acids, a test sample

and a control sample. The control sample of nucleic acids comprises at least 20 distinct nucleic acids such that each of these nucleic acids are of known sequence and known amount. The hybridization patters of the target nucleic acids are detected. Specifically, Brown teaches a method of detecting differential expression of each of a plurality of genes in a first cell type with respect to expression of the same genes in a second cell type (col 4, lines 52-55). Brown teaches that there is "first produced fluorescent-labeled cDNAs from mRNAs isolated from the two cells types, where the cDNAs from the first and second cell types are labeled with first and second different fluorescent reporters (col 4, lines 55-60)(limitations of Claim 5, 9, 10). Brown teaches simultaneously adding "a mixture of the labeled cDNAs from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array (col 4, lines 60-65)(limitations of Claim 14). The array is then analyzed for hybridization patterns by detection of fluorescence (col 4, lines 65-67). Brown teaches that the relative expression of known genes in the two cell types may be determined by the observed fluorescence emission color of each spot (col 5, lines 4-8)(limitations of Claim 13). In a specific example provided by Brown, a 0.5 cm x 0.5 cm microarray of 24 cDNA clones, where the microarray was hybridized simultaneously with total cDNA from wild type Arabidopsis plant labeled with a green fluorophore and total cDNA from a transgenic Arabidopsis plant labeled with a red fluorophore (col 5, lines 46-55, Figure 8)(limitations of Claim 6). Two micrograms of the cDNA products from each type of plant were pooled together and hybridized to the cDNA clone array, known amount of the pool of control set of target nucleic acids (col 17, lines 65-68). As provided in

Example 2, the genes "equally expressed in wild type and the transgenic Arabidopsis appeared yellow due to equal contributions of the green and red fluorescence to the final signal. The does are different intensities of yellow indicating various levels of gene expression, indicating in the control sample (wild type sample), 23 of the known cDNA clones were present to some extent (limitations of Claim 1, 2). A single cDNA clone representing the transcription factor HAT4, expressed in the transgenic line of Arabidopsis but not detectably expressing in wild type, appears as a red dot, indicating that the concentration of the test target nucleic acid, namely wild type, would be minimal (limitations of Claim 16). In the event that the transgenic plant sample was considered to be the control sample, all of the spots (probe nucleic acids present on the array) would have appeared in the control sample (limitations of Claim 3). With respect to Claim 4, in the event that "the same label" is deemed to encompass fluorescent labels, both pools of nucleic acids were labeled with the same label, a fluorescent label, as opposed to a radioactive or calorimetric detection means. Brown teaches that the first two and the last four elements of each array are positive controls for the detection step.

Brown does not explicitly teach contacting the test and control pools sequentially or to distinct arrays.

However, with respect to Claim 7, 15, Brown, in Example 3, specifically teaches that oligonucleotides where separately contacted with different arrays, namely quadrants. Therefore, applying the teachings of Brown in Example 2 with the teachings in Example 3, the skilled artisan would have clearly recognized that contacting distinct arrays, a first and a second array, with the different pools, namely a control and a target

pool, would obtain equivalent results. The ordinary artisan would have therefore realized that whether the samples were hybridized simultaneously or sequentially would not alter the expected benefit of the method of Brown. Furthermore, contacting the samples to different arrays would have similarly been merely a matter of choice.

9. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al (US Pat. 6,040,138, March 21, 2000) in view of Brown et al. (US Pat. 5,807,522, September 15, 1998).

Lockhart et al. (herein referred to as Lockhart) teaches an array based method of monitoring the expression levels of a multiplicity of genes. Lockhart teaches providing a pool of target nucleic acids comprising mRNA transcripts of one or more of said genes, or nucleic acids derived from the mRNA transcripts; hybridizing the pool of nucleic acids to an array of oligonucleotide probes immobilized on a surface (col 2, lines 55-60)(limitations of Claim 6, 8, 14). Lockhart teaches that the pool of nucleic acids may be labeled before, during or after hybridization with fluorescence labels (col 3, lines 55-60). Lockhart teaches fluorescence labels allow quantification of fluorescence from the hybridized fluorescently labeled nucleic acid (col 3, lines 60-65)(limitations of claim 4, 5). The pool of target nucleic acid may be total poly A+ mRNA or cDNA generated by reverse transcription of the RNA or second strand cDNA (col 4, lines 7-15)(limitations of Claim 9, 10). Lockhart teaches absolute quantification may be accomplished by inclusion of known concentrations of one or more target nucleic acids (e.g. control nucleic acids such as Bio B or with known amounts of the target nucleic acids

themselves) and referencing the hybridization intensities of unknowns with the known target nucleic acids (col 7-8, lines 65-5). Simple quantification of the fluorescence intensity for each probe is determined by measuring probe signal strength at each location on the high density array (col 23, lines 45-50)(limitations of Claim 13, 16). Lockhart teaches the importance of using normalization controls. Normalization probes can be localized at any position in the array or at multiple positions throughout the array to control for spatial variation in hybridization efficiently, especially at the corners or edges of the array as well as in the middle (col 16, lines 1-30). Lockhart teaches adding the normalization control probes complementary to control sequences in a known concentration to the sample (col 24, lines 10-15). This allows for controlling variations in hybridization conditions (col 24, lines 20-23). Lockhart teaches that the methods permitting monitoring of expression of a large number of genes simultaneously and effective significant advantages in reduced labor, cost and time (col 4, lines 55-60).

Lockhart does not specifically teach spiking the sample with at least 20 control nucleic acids of known sequence and in known amount. Moreover, Lockhart does not specifically teach sequential or distinct array analysis.

However Brown et al. (herein referred to as Brown) teaches an array based hybridization assay which contacts an array with two sets/pools of target nucleic acids, a test sample and a control sample. The control sample of nucleic acids comprises at least 20 distinct nucleic acids such that each of these nucleic acids are of known sequence and known amount. The hybridization patters of the target nucleic acids are detected. Specifically, Brown teaches a method of detecting differential expression of

each of a plurality of genes in a first cell type with respect to expression of the same genes in a second cell type (col 4, lines 52-55). Brown teaches that there is "first produced fluorescent-labeled cDNAs from mRNAs isolated from the two cells types, where the cDNAs from the first and second cell types are labeled with first and second different fluorescent reporters (col 4, lines 55-60)(limitations of Claim 5, 9, 10). Brown teaches simultaneously adding "a mixture of the labeled cDNAs from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array (col 4, lines 60-65)(limitations of Claim 14). The array is then analyzed for hybridization patterns by detection of fluorescence (col 4, lines 65-67). Brown teaches that the relative expression of known genes in the two cell types may be determined by the observed fluorescence emission color of each spot (col 5, lines 4-8)(limitations of Claim 13). In a specific example provided by Brown, a 0.5 cm x 0.5 cm microarray of 24 cDNA clones, where the microarray was hybridized simultaneously with total cDNA from wild type Arabidopsis plant labeled with a green fluorophore and total cDNA from a transgenic Arabidopsis plant labeled with a red fluorophore (col 5, lines 46-55, Figure 8)(limitations of Claim 6). Two micrograms of the cDNA products from each type of plant were pooled together and hybridized to the cDNA clone array, known amount of the pool of control set of target nucleic acids (col 17, lines 65-68). As provided in Example 2, the genes "equally expressed in wild type and the transgenic Arabidopsis appeared yellow due to equal contributions of the green and red fluorescence to the final signal. The does are different intensities of yellow indicating various levels of gene expression, indicating in the control sample (wild type sample),

23 of the known cDNA clones were present to some extent (limitations of Claim 1, 2). A single cDNA clone representing the transcription factor HAT4, expressed in the transgenic line of Arabidopsis but not detectably expressing in wild type, appears as a red dot, indicating that the concentration of the test target nucleic acid, namely wild type, would be minimal (limitations of Claim 16). In the event that the transgenic plant sample was considered to be the control sample, all of the spots (probe nucleic acids present on the array) would have appeared in the control sample (limitations of Claim 3). With respect to Claim 4, in the event that "the same label" is deemed to encompass fluorescent labels, both pools of nucleic acids were labeled with the same label, a fluorescent label, as opposed to a radioactive or calorimetric detection means. However, with respect to Claim 7, 15, Brown, in Example 3, specifically teaches that oligonucleotides where separately contacted with different arrays, namely quadrants. Brown teaches that the first two and the last four elements of each array are positive controls for the detection step.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the array based method of Lockhart which includes spiking the sample with control nucleic acids and/or using control nucleic acids with the method of Brown which places a control spot in each of the corners of the quadrants of the array. While Lockhart specifically teaches "normalization probes can be localized at any position in the array or at multiple positions throughout the array to control for spatial variation in hybridization efficiently, especially at the corners or edges of the array as well as in the middle" (col 16, lines 1-30), Lockhart does not specifically teach using 20

distinct target nucleic acids. Brown, however, teaches using nucleic acids of more than 20 distinct control nucleic acids to enable detection and quantification. Therefore, using the teachings of both Lockhart and Brown, the ordinary artisan would have been motivated to have designed arrays which contained six controls for each quadrant of the array as taught by Brown. Therefore, in the event that the ordinary artisan used a 1.8 cm x 1.8 cm array as illustrated in Figure 6 of Brown, which contains 8 quadrants, the array would contain 48 control spots. Therefore, using the teachings of Lockhart, "these normalization controls are probes complementary to control sequences added in a known concentration to the sample". Moreover, designing of larger arrays or arrays with smaller quadrants would require larger amounts of control spots. The ordinary artisan would have been motivated to have generated larger arrays for the express benefit of assaying for larger numbers of genes and nucleic acid sequences with less cost, and materials. Therefore, an array of more than 50 control nucleic acids would have been obvious.

Moreover, it would have been prima facie obvious to one of ordinary skill in the art to have applied the teachings of Brown in Example 2 with the teachings in Example 3. The skilled artisan would have clearly recognized that contacting distinct arrays, a first and a second array, with the different pools, namely a control and a target pool, would obtain equivalent results. The ordinary artisan would have therefore realized that whether the samples were hybridized simultaneously or sequentially would not alter the expected benefit of the method of Brown. Furthermore, contacting the samples to different arrays would have similarly been merely a matter of choice.

10. Claims 1, 4-10, 12-16, 26-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bao et al. (US Pat. 6,251,601, filed February 2, 1999).

Bao et al. (herein referred to as Bao) teaches a method of simultaneous measurement of gene expression and genomic abnormalities using nucleic acid microarrays. Bao teaches a method comprising contacting an array with a plurality of probes with a test set and a control set of target nucleic acids. The control set comprises at least 20 distinct control target nucleic acids of known sequence and known amount and all of said probe nucleic aids are present on said array are present in the control set. Specifically, Bao teaches contacting at least three labeled probes nucleic acid populations with an array such that each of the populations are labeled in a fluorescent color (col. 6, lines 35-45)(limitations of Claim 4-5). All of the populations are labeled with a fluorescent label (limitations of Claim 4). Moreover, each of the populations is labeled with a different fluorescent color (limitations of Claim 5). Bao teaches that "measurement and comparison of hybridization of message, genomic and reference nucleic acids at the same target elements provides the simultaneous assessment of expression and genomic changes." This inherently implies that each reference nucleic acid is present on the array. As seen in Figure 2d-f, bar graphs of the ratios of cDNA and genomic to reference sequences for various genes is exemplified. Bao teaches that an array of 31 target elements is exemplary, but the number of target elements and the complexity of the nucleic acids determines the density (cool. 8, lines 1-5). Bao teaches that the reference nucleic acids can be "spiked" to include a known

amount of a particular genomic or cDNA sequence, i.e. known amount and known sequence for each of the controls. Bao teaches that the quantities of each labeled tissue nucleic acid and reference nucleic acid to be used are preferably in the range of about 100ng to about 1ug (col. 13, lines 25-31)(limitations of Claim 26, 30). The tissue and reference nucleic acid populations are hybridized to the array under suitable hybridization conditions (col. 13, lines 32-35). Bao analyzes the microarray by determining the intensity of each of the target spots. Bao teaches that the value "D" is for the reference intensity (col. 17, lines 22-25). Bao provides numerous formulas for determining the normalized presence of the nucleic acids (col. 18). For the specific example provided by Bao, the fluorescence ration for the Colo 320 compared to the reference is depicted in Table 3. Table 3 illustrates that the fluorescence of each of the targets on the array were present in the control set since a ratio was determined. Bao teaches that the gene amplification observed with three probes hybridized simultaneously to one chip was similar to that obtained by separate hybridizations of DNAs onto separate chips (col. 28, lines 25-28). Bao teaches that "with the use of total human genomic DNA as a reference for expression analysis in the methods of the invention, the expression profiles of different samples can be compared even if the assays are carried out separately and independently" (col. 34, lines 25-32)(limitations of Claim 6-8, 28-29).

The skilled artisan would have clearly recognized that contacting distinct arrays, a first and a second array, with the different pools, namely a control and a target pool, would obtain equivalent results. The ordinary artisan would have therefore realized that

whether the samples were hybridized simultaneously or sequentially would not alter the expected benefit of the method of Bao. Furthermore, contacting the samples to different arrays would have similarly been merely a matter of choice (limitations of Claims 14-15).

Moreover, the skilled artisan would have been motivated to have generated an array based method with at least 50 distinct control target nucleic acids in the event that the specific experiment involved at least 50 or 100 distinct targets. Bao suggests that an array of 300 targets would have been a matter of choice. Therefore, the density of an array is merely a matter of preference and experimental design.

Conclusion

11. No claims allowable over the art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
September 26, 2005